HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Supprelin® LA safely and effectively. See full prescribing information for Supprelin LA.

Supprelin LA (histrelin acetate) subcutaneous implant
Initial U.S. Approval: 2007

----------INDICATIONS AND USAGE----------

Supprelin LA is a gonadotropin releasing hormone (GnRH) agonist indicated for the treatment of children with central precocious puberty (CPP) (1).

----------DOSAGE AND ADMINISTRATION----------

The recommended dose of Supprelin LA is one implant every 12 months. The implant is inserted subcutaneously in the inner aspect of the upper arm and provides continuous release of histrelin acetate for 12 months of hormonal therapy (2.).

----------DOSAGE FORMS AND STRENGTHS----------

Supprelin LA is available as a 50 mg histrelin acetate subcutaneous implant which delivers approximately 65 mcg histrelin acetate per day over 12 months (3).

----------CONTRAINDICATIONS----------

- History of hypersensitivity to gonadotropin releasing hormone (GnRH) or GnRH analogs (4).
- Pregnancy: Supprelin LA can cause fetal harm when used during pregnancy (4).

----------WARNINGS AND PRECAUTIONS----------

Initial Agonistic Action: Initial transient increases of estradiol and/or testosterone may cause a temporary worsening of symptoms (5.1).

----------ADVERSE REACTIONS----------

- The most common adverse reaction is implant site reaction (51.1%), including complications related to the insertion or removal of the implant (6).
- Adverse events related to suppression of endogenous sex steroid secretion may occur (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Indevus Pharmaceuticals at 1-888-282-5372 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

----------USE IN SPECIFIC POPULATIONS----------

Use of Supprelin LA in children less than 2 years of age is not recommended (8.4).

See 17 **for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.**

Revised: 07/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Supprelin LA (histrelin acetate) subcutaneous implant is indicated for the treatment of children with central precocious puberty (CPP).

Children with CPP (neurogenic or idiopathic) have an early onset of secondary sexual characteristics (earlier than 8 years of age in females and 9 years of age in males). They also show a significantly advanced bone age that can result in diminished adult height attainment.

Prior to initiation of treatment a clinical diagnosis of CPP should be confirmed by measurement of blood concentrations of total sex steroids, luteinizing hormone (LH) and follicle stimulating hormone (FSH) following stimulation with a GnRH analog, and assessment of bone age versus chronological age. Baseline evaluations should include height and weight measurements, diagnostic imaging of the brain (to rule out intracranial tumor), pelvic/testicular/adrenal ultrasound (to rule out steroid secreting tumors), human chorionic gonadotropin levels (to rule out a chorionic gonadotropin secreting tumor), and adrenal steroids to exclude congenital adrenal hyperplasia.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of Supprelin LA is one implant every 12 months. Each implant contains 50 mg histrelin acetate. The implant is inserted subcutaneously in the inner aspect of the upper arm and provides continuous release of histrelin acetate (65 mcg per day) for 12 months of hormonal therapy. Supprelin LA must be removed after 12 months of therapy (the implant has been designed to allow for a few additional weeks of histrelin acetate release in order to allow flexibility of medical appointments). At the time an implant is removed, another implant may be inserted to continue therapy. Discontinuation of Supprelin LA should be considered at the discretion of the physician and at the appropriate time point for the onset of puberty (approximately 11 years for females and 12 years for males).

2.2 Insertion Procedure

The implant should be kept refrigerated (2-8°C) until the day of the procedure. The insertion tool, supplied as part of the implantation kit, does not require refrigeration. All other supplies necessary to insert and/or remove the implant will be provided in the implantation kit.

It is important to use aseptic techniques to minimize any chance of infection. Sterile gloves are required for the insertion procedure and subsequent removal of the implant.

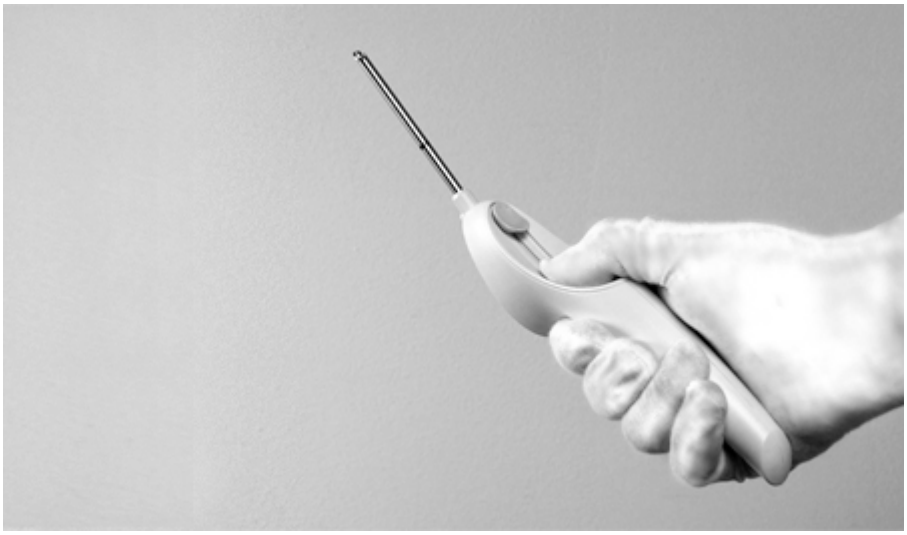
The implant is inserted using the procedure outlined below:

Identifying the Insertion Site

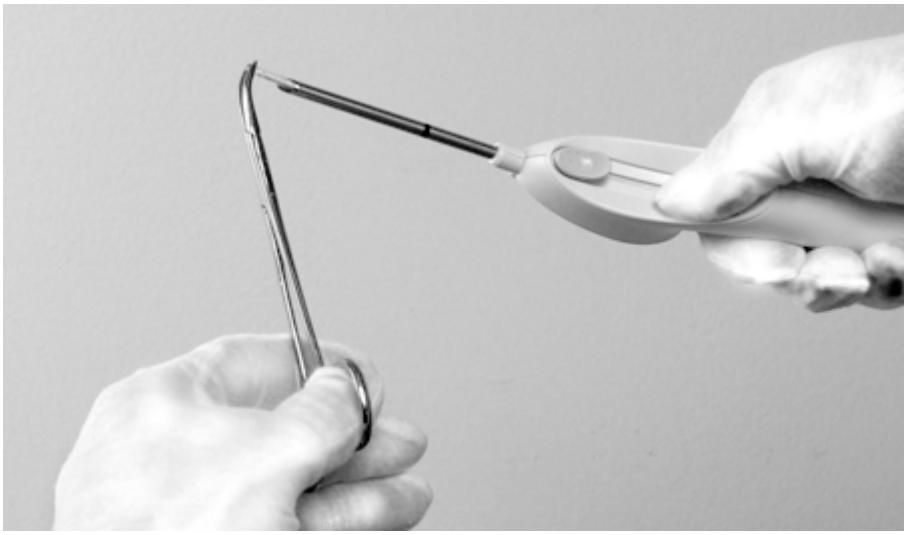
The patient should be on his/her back, with the arm least used (e.g., left arm for a right-handed person) flexed so the physician has ready access to the inner aspect of the upper arm. Prop the arm with pillows so the patient can easily hold that position. The optimum site for insertion is approximately half way between the shoulder and the elbow and in the crease between the bicep and triceps.

Loading the Insertion Tool

Load the insertion tool prior to prepping the insertion field and insertion site. Remove the insertion tool from its sterile bag. The tool is shipped with the cannula fully extended. Verify this by inspecting the position of the green retraction button. The button should be all the way forward, towards the cannula, away from the handle. Remove the metal band from the vial, remove the rubber stopper, and use a mosquito clamp to grasp either tip of the implant. Avoid grabbing or clamping the middle of the implant to prevent distortion of the implant.

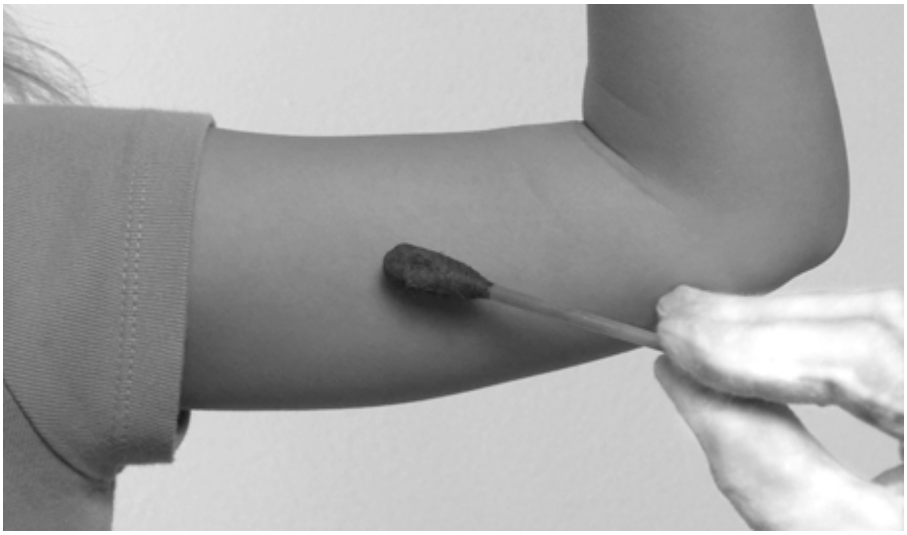


Insert the implant into the cannula of the insertion tool. The implant will rest in the cannula so that just the tip is visible at the bottom of the bevel.



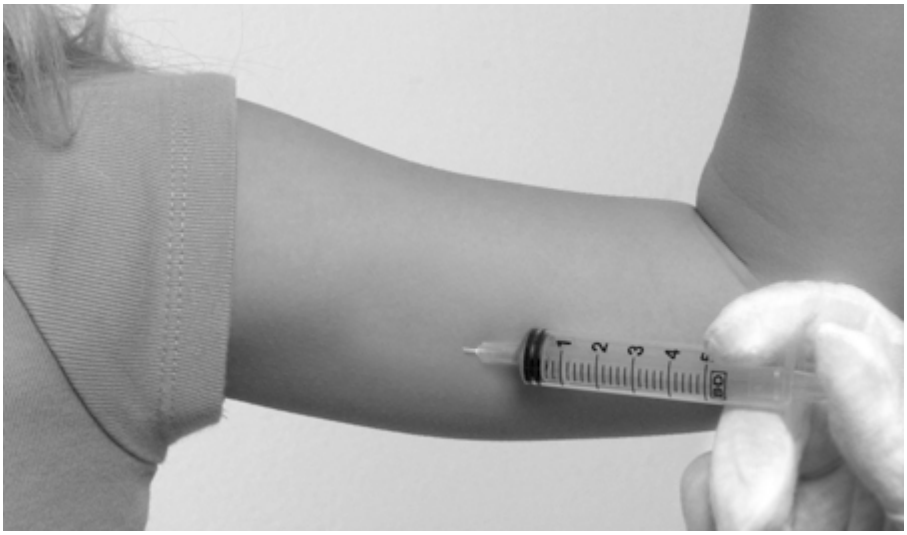
Inserting the Implant

1. Swab the insertion area with povidone-iodine swabs, then lay a fenestrated drape over the insertion site (for clarity of illustration, the accompanying photos do not show the drape).



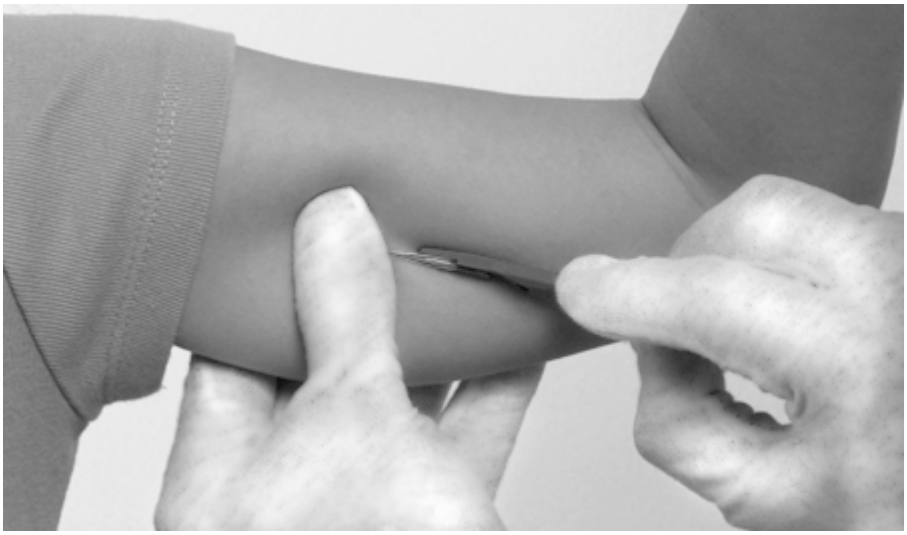
Anesthetic

2. The method of anesthesia (i.e., local, conscious sedation or general) utilized should be determined at the discretion of the physician and/or surgeon performing the procedure. After determining the absence of known allergies to the anesthetic agent, a topical lidocaine or lidocaine/epinephrine cream can be used to anesthetize the area prior to injection of local anesthetic. Inject a few milliliters of the anesthetic, starting at the planned incision site, then infiltrating up to the length of the implant, 32 mm, in a fan-like fashion.



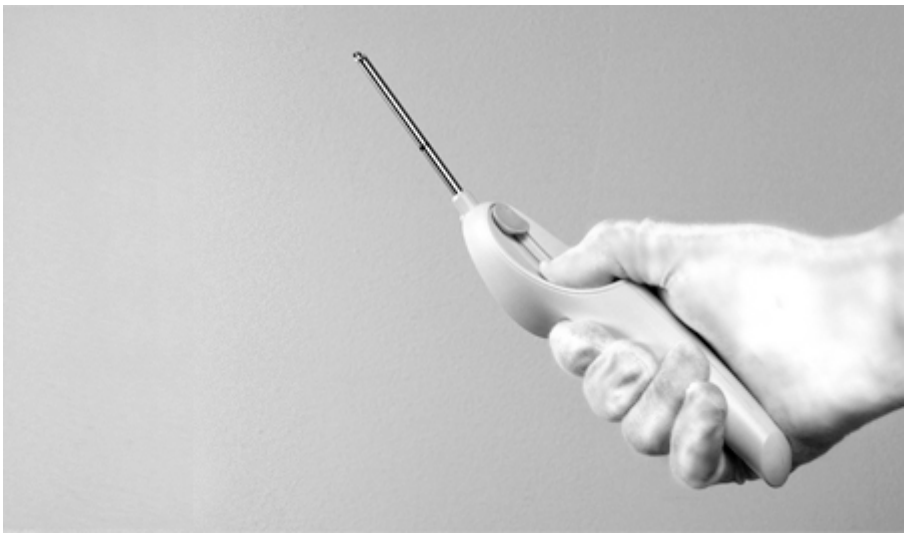
Incision

3. Using a scalpel, make a 2-3 mm incision immediately subcutaneous and perpendicular to the shoulder.

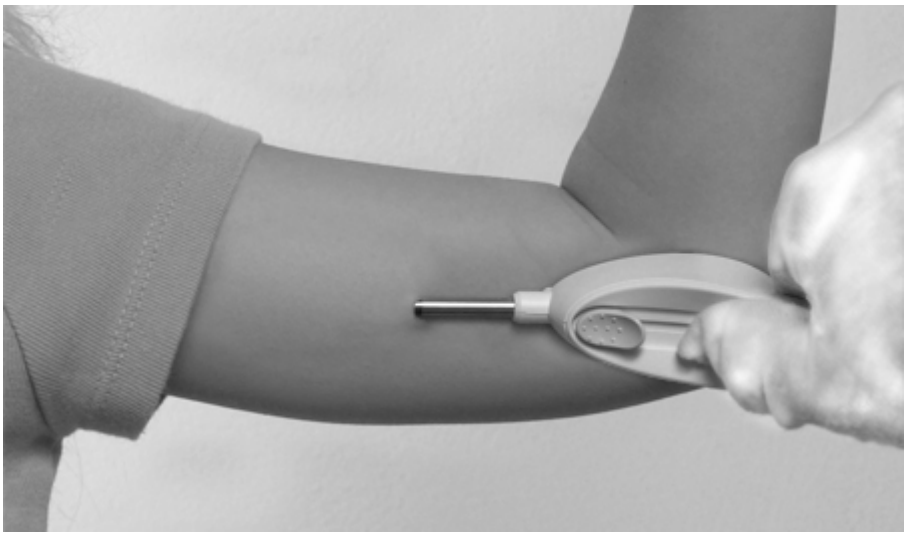


Insertion

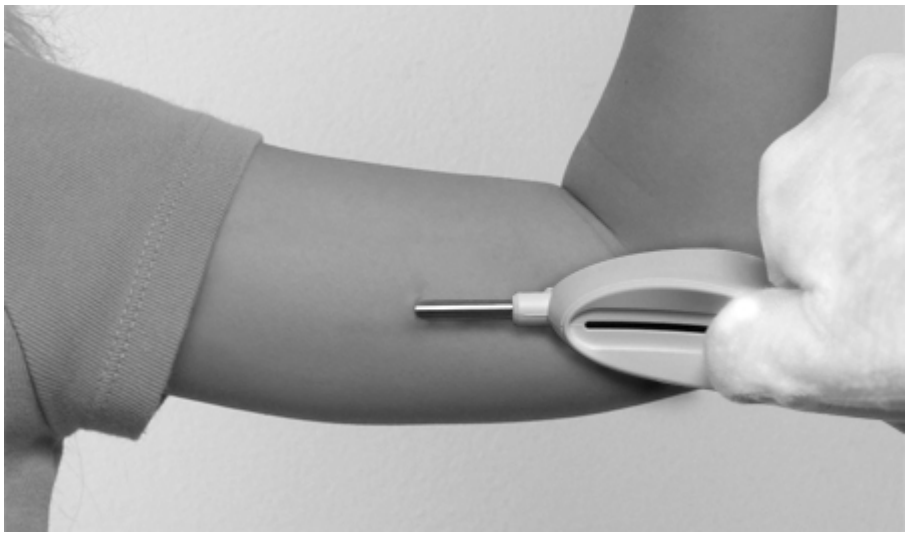
4. Grasp the insertion tool by its handle, as shown.



5. Insert the tip of the insertion tool into the incision with the bevel up and advance the tool subcutaneously along the path of the anesthetic, up to the inscribed line on the cannula. Pull back the tool about an inch, almost to the tip, while keeping the insertion path just immediately subcutaneous. Keep the insertion tool extended and locked while pulling back the insertion tool. Push the tool back into the arm, up to the black line. This will create a "pocket" for the implant. To ensure subcutaneous placement, the insertion tool should visibly raise the skin at all times during insertion. Be sure that the insertion tool doesn't enter the muscle tissue.



6. Hold the insertion tool in place as you move your thumb to the green retraction button. Press the button down to release the locking mechanism, then draw the button back to the back stop, all the while holding the tool in place. The cannula will withdraw from the incision, leaving the implant in the dermis. Withdraw the insertion tool from the incision. Release of the implant can be checked by palpation.



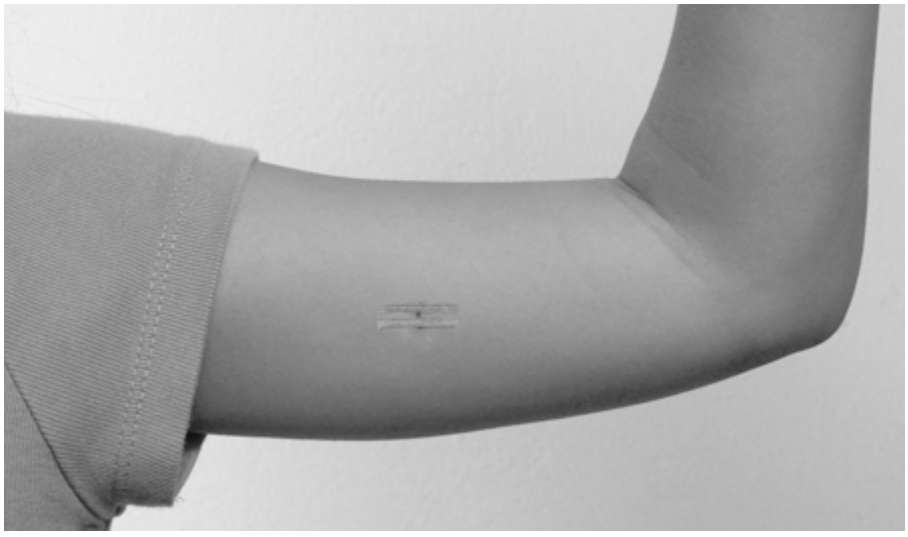
NOTE: Do not try to push the tool in deeper once the retraction process has started to avoid severing the implant. If you wish to re-start the process, withdraw the tool, grasp the implant by the tip to extract it, reset the retraction button to its most forward position, reload the implant, and start again.

Alternatively, the implant can be inserted manually by creating a pocket with the mosquito clamp large enough to allow insertion of the implant. Procedures for incision and closure are the same as instructed above.

After placement, sterile gauze may be used to apply pressure briefly to the insertion site to ensure hemostasis.

Closing the Incision

7. To close the incision, use one or two sutures (optional), knots facing inside the incision. Apply a light coating of antibiotic ointment directly onto the incision. The incision can also be closed with two surgical strips. Apply one or two of the gauze pads over the incision and secure with an adhesive elastic bandage.

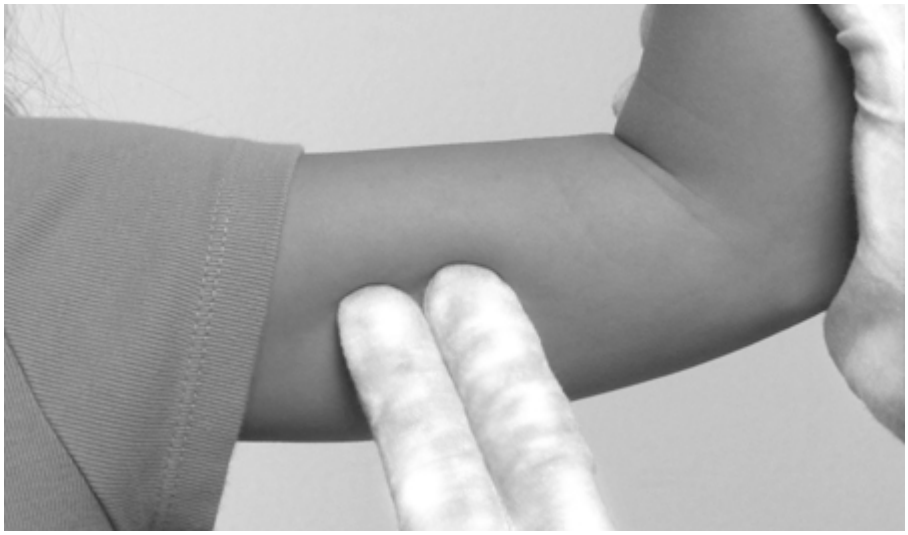


2.3 Removal Procedure and New Implant Insertion

Supprelin LA must be removed after 12 months of therapy. The techniques and instruments required are the same as for implantation. Assemble all the necessary implements prior to the procedure.

Locating the Implant

The implant may be located by palpating the area near the incision from the prior year. Generally, the implant is readily palpated. Press the distal end of the implant to determine the proximal tip's location relative to the old incision.



In the event the implant is difficult to locate, ultrasound can be used. If ultrasound fails to locate the implant, other imaging techniques such as CT or MRI may be used to locate it **(**plain films are not recommended as **the implant is not radiopaque**).

Preparing the Site

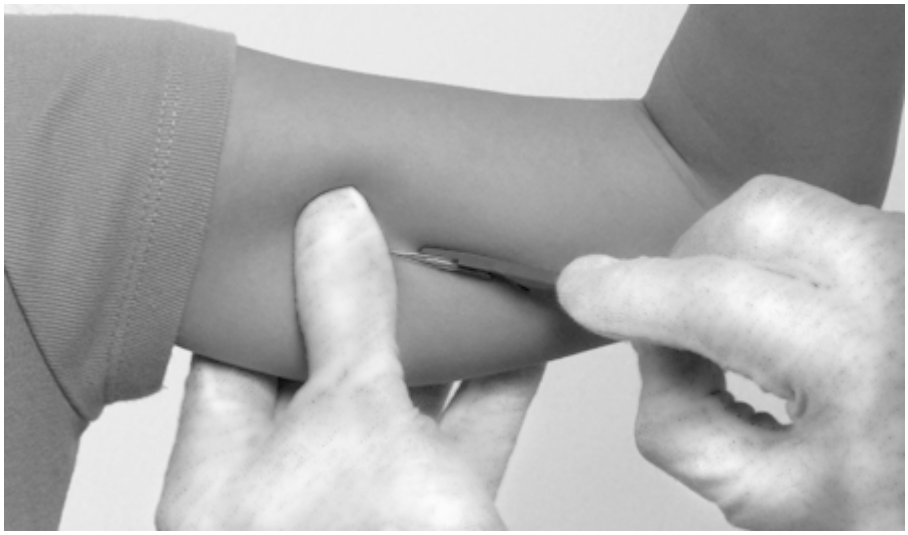
1. Patient position and site preparation are the same as for the initial insertion. Swab the area above and around the implant with the povidone-iodine swabs. Drape the area with a fenestrated drape.

Anesthetic

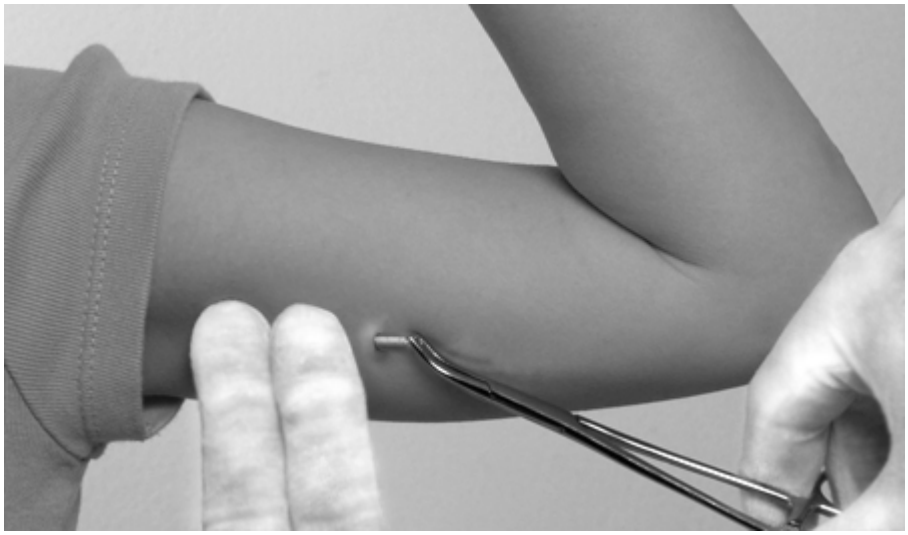
2. After determining the absence of known allergies to the anesthetic agent, press down on the implant tip furthest from the old incision to determine the location of the tip closest to the incision. Inject a small amount of lidocaine/epinephrine at the tip near the incision, then advance the needle along the length, but beneath the implant, steadily injecting a small amount of anesthetic along the way. The anesthetic will raise the implant up within the dermis. If you are inserting a new implant, you have the option of either placing the new one in the same "pocket" as the removed one, or using the same incision; insert the new implant in the opposite direction. If placing the new implant in the opposite direction, inject a few milliliters of the anesthetic, starting at the planned incision site, then infiltrating up to the length of the location of the new implant, 32 mm, in a fan-like fashion. Apply anesthetic prior to removal of the old implant.

Incision/Implant Removal

3. Using a scalpel, make a 2-3 mm incision near the tip and about 1-2 mm deep. Generally, the tip of the implant will be visible through a pseudocapsule of tissue. If not, push down on the distal tip of the implant and massage it forward towards the incision. Carefully nick the pseudocapsule to reveal the polymer tip. Insert the mosquito clamp into the hole created in the pseudocapsule and expand by opening the clamp. Widening the opening of the pseudocapsule helps ease the extraction of the old implant.



4. Grasp the tip with the mosquito clamp and extract the implant.



5. Dispose of the implant in a proper manner, treating it like any other bio-waste.

If inserting a new implant - proceed according to "Loading the Insertion Tool", "Insertion", and "Closing the Incision" sections above.

The new implant may be placed through the same incision site. Alternatively, the contralateral arm may be used.

6. Provide the patient with the Patient Labeling material.

3 DOSAGE FORMS AND STRENGTHS

Supprelin LA is a sterile, nonbiodegradable, diffusion-controlled reservoir drug delivery system designed to deliver histrelin acetate continuously for 12 months after subcutaneous implantation. The sterile histrelin acetate implant contains 50 mg histrelin acetate and delivers approximately 65 mcg histrelin acetate per day over 12 months.

4 CONTRAINDICATIONS

Supprelin LA is contraindicated in patients who are hypersensitive to gonadotropin releasing hormone (GnRH) or GnRH agonist analogs.

Supprelin LA is contraindicated in females who are or may become pregnant while receiving the drug. Supprelin LA may cause fetal harm when administered to pregnant patients. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. The possibility exists that spontaneous abortion may occur *[see USE IN SPECIFIC POPULATIONS (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Initial Agonistic Action

Supprelin LA, like other GnRH agonists, initially causes a transient increase in serum concentrations of estradiol in females and testosterone in both sexes during the first week of treatment. Patients may experience worsening of symptoms or onset of new symptoms during this period. However, within 4 weeks of histrelin therapy, suppression of gonadal steroids occurs and manifestations of puberty decrease.

5.2 Implant Insertion/Removal Procedure

Implant insertion is a surgical procedure and it is important that the insertion instructions are followed to avoid potential complications. The insertion and removal of the implant should be done aseptically. Proper surgical technique is critical in minimizing adverse events related to the insertion and the removal of the histrelin implant. On occasion, localizing and/or removal of implant products have been difficult and imaging techniques were used, including ultrasound, CT, or MRI (note: the histrelin implant is not radiopaque). Rare events of spontaneous extrusion of the implant have been observed in clinical trials. During Supprelin LA treatment, patients should be evaluated for evidence of clinical and biochemical suppression of CPP manifestations (see Section 5.3, Monitoring and Laboratory tests). Detailed instructions on the insertion and removal procedures of the implant are provided above *[see DOSAGE AND ADMINISTRATION (2.2, 2.3)]*.

5.3 Monitoring and Laboratory Tests

LH, FSH and estradiol or testosterone should be monitored at 1 month post implantation then every 6 months thereafter. Additionally, height (for calculation of height velocity) and bone age should be assessed every 6-12 months.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

The most common adverse reactions with Supprelin LA involved the implant site. Local reactions after implant insertion include bruising, pain, soreness, erythema and swelling.

During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the natural stimulatory effect of the drug. Therefore, an increase in clinical signs and symptoms may be observed *[see WARNINGS AND PRECAUTIONS (5.1)]*.

6.2 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Supprelin LA in children with CPP was evaluated in two single-arm clinical trials conducted in a total of 47 patients (44 females and 3 males) over a period of time ranging from 9 to 18 months. The most commonly reported adverse reaction was implant site reaction, which was reported by 24 of 47 (51.1%) patients. Implant site reaction includes discomfort, bruising, soreness, pain, tingling, itching, implant area protrusion and swelling. Two subjects experienced a serious adverse reaction: 1 subject who coincidentally had Stargardt's Disease experienced amblyopia and 1 subject had a benign pituitary tumor (pituitary adenoma). One subject discontinued the study due to an adverse reaction of infection at the implant site. There were no clinically meaningful findings in standard clinical hematology and chemistry tests and/or in vital signs. The incidence of implantation adverse events reported by more than 2 patients are summarized in Table 1.

Table 1: Incidence of implantation adverse reactions reported by ≥2 patients treated with Supprelin LA in both clinical trials

Adverse Reactions	**N=47 N (%)**
Implant site reaction	24 (51.1)
Keloid scar	3 (6.4)
Scar	3 (6.4)
Suture related complication	3 (6.4)
Application site pain	2 (4.3)
Post procedural pain	2 (4.3)

The following adverse reactions were reported as possibly related or related in 1 patient each: wound infection, breast tenderness, dysmenorrhea, epistaxis, erythema, feeling cold, gynecomastia, headache, menorrhagia, migraine, mood swings, pituitary tumor benign, pruritus, weight increased, disease progression and influenza-like illness. The adverse reaction metrorrhagia was reported as possibly related or related in 2 patients.

7 DRUG INTERACTIONS

Overview: No formal drug-drug, drug-food, or drug-herb interaction studies were performed with Supprelin LA.

Drug-Laboratory Interactions: Therapy with Supprelin LA results in suppression of the pituitary-gonadal system. Results of diagnostic tests of pituitary gonadotropic and gonadal functions conducted during and after

Supprelin LA therapy may be affected. Supprelin LA decreased mean serum insulin-like growth factor-1 (IGF-1) levels by approximately 11% in one study (Study 1). Supprelin LA increased the serum concentration of dehydroepiandrosterone (DHEA) in 8 of 36 patients in another study (Study 2).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy category X [*see CONTRAINDICATIONS (4)*].
Supprelin LA is contraindicated in females who are, or may become, pregnant while receiving the drug. Supprelin LA can cause fetal harm when administered to a pregnant patient. The possibility exists that spontaneous abortion may occur.

Animal Data: Major fetal abnormalities were observed in rabbits at 3 times human therapeutic exposure but not in rats after administration of histrelin acetate throughout gestation. There was dose-related increased fetal mortality during organogenesis in both rats given 1, 3, 5 or 15 mcg per kg per day (at less than therapeutic exposures using body surface area comparisons, based on a 65 mcg per day human dose) and in rabbits at 20, 50 or 80 mcg per kg per day (at 3 times human exposure using body surface area comparisons, based on a 65 mcg per day dose in humans).

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 2 years have not been established. The use of Supprelin LA in children under 2 years is not recommended.

10 OVERDOSAGE

There have been no reports of overdose in Supprelin LA clinical trials. High doses of histrelin acetate injection in animal studies were generally associated only with effects attributed to the expected pharmacology. The method of drug delivery makes accidental or intentional overdosage unlikely.

11 DESCRIPTION

Supprelin LA (histrelin acetate) subcutaneous implant contains a synthetic nonapeptide analog of the naturally occurring gonadotropin releasing hormone (GnRH) that possesses a greater potency than the natural sequence hormone. The chemical name of histrelin acetate is:

L-Pyroglutamyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-N-benzyl-D-histidyl-L-leucyl-L-arginyl-L-proline N-ethylamide, acetate salt.

The molecular formula for histrelin acetate is $C_{66}H_{86}N_{18}O_{12}$ x 2 CH_3COOH and its molecular weight is 1443.70 (or 1323.52 as free base). Histrelin is also chemically described as 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-Nt-benzyl-D-histidyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide diacetate. The chemical structure of the free base (histrelin) is represented below in Figure 1.

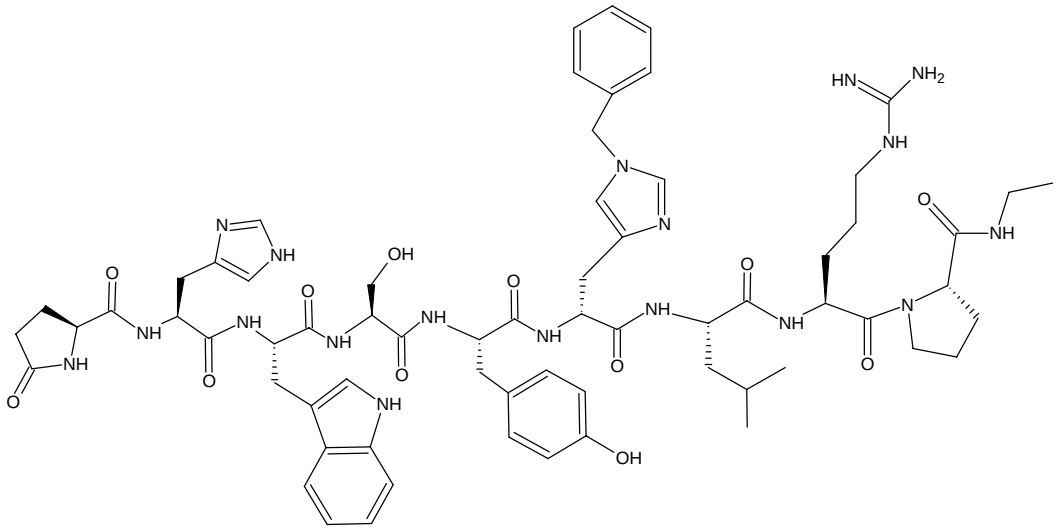


Figure 1. Structure of histrelin

The Supprelin LA implant looks like a small thin flexible tube. The sterile implant consists of a 50-mg histrelin acetate drug core inside a non-biodegradable, 3.5 cm by 3 mm, cylindrical hydrogel reservoir (Figure 2).

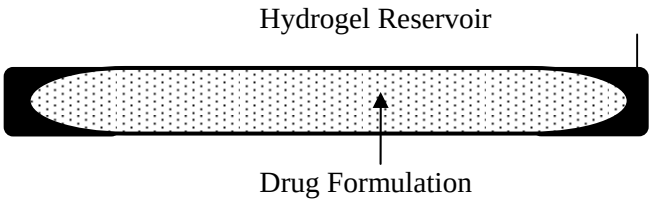


Figure 2. Histrelin Implant diagram (not to scale)

The drug core also contains the inactive ingredient stearic acid NF. The hydrogel reservoir is a cartridge composed of 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, trimethylolpropane trimethacrylate, benzoin methyl ether, Perkadox-16, and Triton X-100. Each hydrated implant is packaged in a glass vial containing 2 mL of 1.8% sodium chloride, sterile solution, so that it is primed for immediate release of the drug upon insertion. The 3.5 mL Type I clear glass vial with the implant is closed with a pre-treated grey Teflon coated stopper and sealed with an aluminum crimp seal.

A single use sterile insertion tool (Trocar) is to be used with Supprelin LA. The insertion tool is enclosed in a sterile bag as part of the implantation kit.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Supprelin LA is a GnRH agonist and an inhibitor of gonadotropin secretion when given continuously. It delivers approximately 65 mcg histrelin acetate per day. Both animal and human studies indicate that following an initial stimulatory phase, chronic, subcutaneous administration of histrelin acetate desensitizes responsiveness of the pituitary gonadotropin which, in turn causes a reduction in ovarian and testicular steroidogenesis.

In humans, administration of histrelin acetate results in an initial increase in circulating levels of LH and FSH, leading to a transient increase in concentration of gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females).

However, continuous administration of histrelin acetate causes a reversible down-regulation of the GnRH receptors in the pituitary gland and desensitization of the pituitary gonadotropes. These inhibitory effects result in decreased levels of LH and FSH.

12.2 Pharmacodynamics

Long-term treatment with histrelin acetate suppresses the LH response to GnRH causing LH levels to decrease to prepubertal levels within 1 month of treatment. As a result, serum concentrations of sex steroids (estrogen or testosterone) also decrease. Consequently, secondary sexual development ceases to progress in most patients. Additionally, linear growth velocity is slowed which improves the chance of attaining predicted adult height.

12.3 Pharmacokinetics

Pharmacokinetics of histrelin after implantation of Supprelin LA was evaluated in a total of 47 children with CPP (11 subjects in Study 1 and 36 subjects in Study 2). Patients were examined at 4 weeks after implant insertion and a few times throughout the treatment period. Median serum histrelin concentrations remained above the limit of quantification for the treatment period. Histrelin acetate levels were sustained throughout the study period for most subjects (Figure 3). The median of maximum serum histrelin concentrations over the study period was 0.43 ng/mL, which is expected to maintain gonadotropins at prepubertal levels. There was no apparent pharmacokinetic difference between naïve subjects to a LHRH agonist treatment and subjects who had previous treatment with a LHRH agonist (Figure 3).

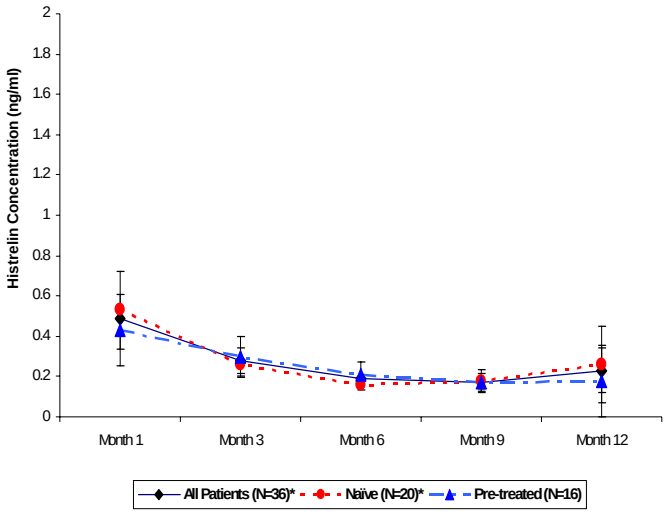


Figure 3. Mean and Standard Deviation of Serum Histrelin Concentrations (ng/mL) Results at Each Visit

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were conducted in rats for 2 years at doses of 5, 25 or 150 mcg/kg per day (up to 11 times human exposures using body surface area comparisons, based on a 65 mcg per day dose in humans) and in mice for 18 months at doses of 20, 200, or 2000 mcg/kg per day (at less than therapeutic exposure to 70 times human exposure using body surface area comparisons, based on a 65 mcg per day dose in humans). As seen with other

GnRH agonists, histrelin injection administration was associated with an increase in tumors of hormonally responsive tissues. There was a significant increase in pituitary adenomas in rats at mid and high doses (2-11 times human exposure based on body surface area comparisons with a 65 mcg per day human dose). There was an increase in pancreatic islet-cell adenomas in treated female rats and a non-dose-related increase in testicular Leydig-cell tumors (highest incidence in the low-dose group). In mice, there was significant increase in mammary-gland adenocarcinomas in all treated females. In addition, there were increases in stomach papillomas in male rats given high doses, and an increase in histiocytic sarcomas in female mice at the highest dose.

Mutagenicity studies have not been performed with histrelin acetate. Saline extracts of implants with and without histrelin acetate were negative in a battery of genotoxicity studies. Fertility studies have been conducted in rats and monkeys given subcutaneous daily doses of histrelin acetate up to 180 mcg/kg per day (up to 13 and 30 times human exposure, respectively using body surface area comparisons, based on a 65 mcg per day human dose) for 6 months and full reversibility of fertility suppression was demonstrated. The development and reproductive performance of offspring from parents treated with histrelin acetate has not been investigated.

14 CLINICAL STUDIES

The efficacy of Supprelin LA in children with CPP has been evaluated in two single arm, open label studies. Study 1 was conducted in 11 pretreated female patients, 3.7 to 11.0 years of age. Study 2 was conducted in 36 patients (33 females and 3 males), 4.5 to 11.6 years of age. Sixteen pretreated and 20 treatment-naïve patients were enrolled in Study 2. Baseline patient characteristics were typical of patients with CPP. Efficacy assessments were similar in both studies and included endpoints that measured the suppression of gonadotropins (luteinizing hormone and follicle stimulating hormone) and gonadal sex steroids (estrogen in girls and testosterone in boys, respectively) on treatment. Other assessments were clinical (evidence of stabilization or regression of signs of puberty) or gonadal steroid-dependent (bone age, linear growth). In Study 2, the primary measure of efficacy was LH suppression.

In Study 2, suppression of LH was induced in all treatment naïve subjects and maintained in all pretreated subjects at month 1 after implantation and continued through month 12 (suppression was defined as a peak LH < 4 mIU/mL following stimulation with the GnRH analog leuprolide acetate).

Secondary efficacy hormone assessments (FSH, estradiol and testosterone) and additional efficacy assessments (bone age advancement, linear growth, clinical progression of puberty) indicated stabilization of disease. Estradiol suppression was present in all 33 girls (100%) through Month 9 and 97% at Month 12. Testosterone suppression was maintained in the three pre-treated males participating in Study 2. The Supprelin LA effect on efficacy endpoints in the Study 1 was consistent with that observed in Study 2.

16 HOW SUPPLIED/STORAGE AND HANDLING

Supprelin LA (NDC 67979-002-01) is supplied in a carton containing 2 inner cartons: a small one for the vial containing the Supprelin LA implant, which is shipped with a cold pack in a polystyrene cooler and must be refrigerated upon arrival, and one for the implantation kit for use with Supprelin LA.

The Supprelin LA implant carton contains an amber plastic pouch. Inside the pouch is a glass vial with a Teflon-coated stopper and an aluminum seal, containing the implant immersed in 2 mL of 1.8% sterile sodium chloride. The sterile insertion tool is part of the implantation kit.

Supprelin LA is stable when refrigerated under the recommended storage conditions (2-8ºC) for up to 2 years. Excursion permitted to 25°C (77°F) for 7 days. Do not freeze. Protect from light. The implantation kit should be stored at room temperature.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (17.4)]

17.1 Initial Agonistic Action

Patients should be advised that a transient worsening of symptoms of puberty or onset of new symptoms may occur initially. However, within 4 weeks of histrelin therapy, complete suppression of gonadal steroids occurs and manifestations of puberty decrease *[see WARNINGS AND PRECAUTIONS (5.1)]*.

17.2 Post-insertion Care

Patients should be instructed to refrain from getting the inserted arm wet for 24 hours and from strenuous exertion of the inserted arm for 7 days after implant insertion to allow the incision to fully close. The adhesive elastic bandage can be removed at that time. The patient should not remove the surgical strips; rather, the strips should be allowed to fall off on their own after several days.

17.3 Common Adverse Reactions

Patients should be advised to report to their physician any severe pain, redness, or swelling in and around the implant site. Infrequently, Supprelin LA may be expelled from the body through the original incision site, rarely without the patient noticing. The patient should be instructed to monitor the incision site until it is healed. The patient should also return for routine checks of their condition and to ensure that Supprelin LA is present and functioning in his/her body *[see WARNINGS AND PRECAUTIONS (5.2)]*.

17.4 FDA-Approved Patient Labeling

Supprelin® LA *[Suh-Preh-Lin El-Ay]*

(histrelin acetate) subcutaneous implant

Read the Patient Information that comes with Supprelin LA before your child begins treatment. This information does not take the place of talking with your child's doctor about their medical condition or treatment.

What is Supprelin LA?

Supprelin LA is an under-the-skin (subcutaneous) implant that contains the medicine histrelin, a gonadotropin releasing hormone (GnRH). Supprelin LA is used for treatment of children with central precocious puberty (CPP).

CPP makes puberty come early in girls (before 8 years of age) and in boys (before 9 years of age). Signs of early puberty include breast enlargement in girls and the appearance of hair in genital area in boys and girls. Supprelin LA works by reducing the amount of sex hormones in the blood to delay early puberty.

Who should not use Supprelin LA?

Your child should not use Supprelin LA if he/she is allergic to gonadotropin releasing hormone (GnRH), GnRH agonist medicines, or anything in the Supprelin LA implant.

Supprelin LA should not be used in:

- children under 2 years of age
- women who are or may become pregnant (Supprelin LA can cause birth defects or loss of the baby).

How is Supprelin LA used?

- Your child's doctor should do tests to make sure your child has CPP before treating your child with Supprelin LA.
- Supprelin LA lasts for 12 months. One implant provides the medicine for 12 months. After 12 months, Supprelin LA must be removed. The doctor may insert a new Supprelin LA at this time to continue treatment.
- Supprelin LA is placed under the skin of the inside of the upper arm. The doctor will temporarily numb the arm of your child, make a small cut, and then place Supprelin LA under the skin. The cut may be closed with stitches or surgical strips and covered with a pressure bandage.
- Your child should keep the arm clean and dry and should not swim or bathe for 24 hours. The bandage can be removed after 24 hours. Do not remove any surgical strips. They will fall off on their own in several days.
- Your child should avoid heavy play or exercise that uses the implanted arm for 7 days. After the cut has healed, your child can go back to his or her normal activities. The doctor will give you complete instructions.
- Keep all scheduled visits to the doctor. Your child's doctor will do regular exams and blood tests to check for signs of puberty. Sometimes the doctor will have to do special examinations, such as ultrasound or MRI, if the Supprelin LA implant is difficult to find under your child's skin.

What are the possible side effects of Supprelin LA?

In the first few weeks of treatment, Supprelin LA can cause a brief increase in some hormones, and during this time you may notice more signs of puberty in your child, including light vaginal bleeding and breast enlargement in girls. Within 4 weeks of treatment, you should see signs in your child that puberty is stopping.

- The most common side effects of Supprelin LA are skin reactions at the place where the implant is inserted. Such reactions may include bruising, soreness, pain, tingling, itching, and swelling. They usually go away without treatment within 2 weeks. Call your child's doctor if your child has bleeding, redness or pain at the insertion site.
- Serious and life-threatening allergic reactions have happened with GnRH medicines (the type of medicine in Supprelin LA).

These may not be all the side effects of Supprelin LA. Ask your child's doctor for more information.

General information about Supprelin LA

This patient labeling summarizes the most important information about Supprelin LA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Supprelin LA that is written for health professionals. You can also visit www.indevus.com on the internet.